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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,822	03/23/2005	Aurelio Orjales Venero	P/4043-153	6533

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OSTROLENK FABER GERB & SOFFEN
1180 AVENUE OF THE AMERICAS
NEW YORK, NY 100368403

EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,822	ORJALES VENERO ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *25* is/are allowed.

6)☐ Claim(s) *33-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This is a RCE of SN 10/511,822.

Claims 1-24, 26-32 have been canceled. Claims 25 and newly added claims 33-37 are pending.

2. Claims 33-34 are rejected under 35 U.S.C. 101 because the claim is wholly inoperable. Please note that when bilastine is dissolved in the selected solvents and heat to reflux, without continuous steps, crystalline form 1 is not obtained. In order for the *claims* to be operable, the critical steps including rate of cooling, solvent removal, seeding etc. wherein crystals can be separated must be included.

3. Claim 35 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916), where the Supreme Court looked to whether the experimentation needed to practice an invention was undue or unreasonable. *Id.* An invention must be described so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). As stated in the MPEP 2164.01(a) "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". The analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *Id.* at 740, *Id.* at 1407. The factors to be considered herein are those set forth as the In re Wands, 8 USPQ 2nd 1400 (1988) decision.

The analysis is applied to the instant case.

Nature of invention

The claim is drawn to a composition having the particular "Form I" of bilastin.

The state of the art and predictability

Per ponderous of factual evidence in "drugs" indicated that the temperature and pressure of pharmaceutical composition processing, such as tableting *would* cause transformation of "forms". See :

Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form …." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

Doelker et al. abstract "…a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (*grinding, tableting, granulations, drying)* may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissoln, rate, bioavailability and even pharmacol. activity."

Otsuke et al. p.852 « …in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

Taday et al. p.831 « …Once in the desired crystalline form, the polymorphic state *may be changed* by incorrect storage or even during tablet preparation" and p.836, figure 8, wherein compound of four form in pharmaceutical composition resulted in similar spectra i.e. form.

(all references attached to previous office actions).

The amount of guidance and working examples

On pages 8-10, description of pharmaceutical composition using conventional carrier were disclosed. In addition, conventional procedure for pharmaceutical formulation including wet processing and dispersion. No where in the specification was a composition of "form I" which is defined explicitly to have all the properties with X-ray, IR etc., that is the composition contain a material that has the same X-ray diffraction pattern essentially as shown on page 2 or IR of figures 1-3. Nowhere in the specification a *composition* of this limitation of the claim was made. In view of the per ponderous of evidence as delineated supra, it is evidenced that crystalline drug does not *automatically* keeps its form in the pharmaceutical composition, thus, *absent of any description or enablement* from the specification, enablement for the "claimed" composition is lacking.

Applicants have amended the specification to include the sentence that "*The making of those pharmaceutical preparations implies procedures in which the active ingredient is not in any case dissolved in a solvent, thus maintaining its crystalline structure*". Were these processing carrier conventional tableting material, powders etc. Then the above per ponderous of evidence using conventional tableting material will result in not maintaining forms still applies. Were these processing carrier unconventional but specific for maintaining crystalline form 1, then, this is *new matter* because it is not within the four corner of the specification as originally filed. Especially the field of solid pharmaceutical excipient art indicated that such processing is more an art then science (see Lanz) and it is difficult to apply standard techniques to identify and predict the transformations [of solid material] (see CMU para bridging p.1-2). Therefore not only the sentence "*The making of those pharmaceutical preparations implies procedures in which the active ingredient is not in any case dissolved in a solvent, thus maintaining its crystalline structure*" did not provide the required guidance of what excipients and how a composition is made which maintains form 1 bilastine; were the sentence intended for any special excipients, it would not be the standard/conventional technique to one having ordinary skill. For new matter inserted in the specification not covered by the original oath, a supplemental oath should be filed see MPEP §602(V).

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 35-37 are rejected under 35 U.S.C. 102(b) as being anticipated by Orjales et al. US 5,877,187, see col. 10, claims 8-21, or *alternatively*;

Claims 35-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Orjales et al. US 5,877,187, in view of Rowland and Tozer supplemented with Corcostegui et al.

(all references attached to previous office actions)

It was evidenced in the conventional teaching in the physiology of the human body that dissolution of the orderly packing i.e. crystal of a drug can occur at several stages of drug

kinetics. The first location is in the formulation stage wherein a liquid dosage such as injection ample, liquid capsule etc. was employed, then the active ingredient i.e. crystal of bilastin is being administered in the dissoluted compound "bilastin" (see for example p.8-9 specification). In this scenario, anticipation is found since both the active ingredient and its outcome are identical to the prior art. The polymorphic form, upon formulation into suspension/liquid or compression would produce the same identical thermodynamically stable product of the prior art see col. 10, claims 8-21. Therefore, the pharmaceutical composition or method of using of claims 36-37 (please note that pharmaceutical composition comprising form 1 bilastine i.e. as claimed is under 112 first paragraph rejection. Pharmaceutical composition comprising bilastine compound with conventional carrier i.e. product as disclosed and enabled which cannot maintain form, thus, would be containing the same compound as the prior art) would have the same dosage, same site of administration and same compound for efficacy being the same as the prior art and anticipation was found.

The other location of dissolution can be expect at either the absorption and distribution stage (see Rowland and Tozer) or at the cellular level wherein the 4-[2-[1-(2- ethoxyethyl)-I H-benzidimazole-2-yl]-1-piperidinyl]ethyl]-α,α-dimethyl- benzeno-acetic acid is inhibiting histamine production. Either stage of the claimed process would be a prima facie obvious modification of the prior art process employed by Orjales et al. '187, because one skilled in the pharmaceutical art would be motivated to modify the prior art method for a purer form (see '187 col. 5-6) especially, such modification is routine practice as *evidenced* by the preclinical trial (see Corcostegui et al.) of the drug.

5. Claim 25 is allowed.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang, Ph. D. whose telephone number is 571-272-0679. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet L. Andres, Ph. D., can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

OACS/Chang
Jan. 7, 2009

/Celia Chang/
Primary Examiner
Art Unit 1625